



Submitting High Quality eCTD Submissions to FDA/OGD

**GPhA/FDA ANDA Labeling Workshop/ USP
User Forum
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FDA Disclaimer

- Views expressed in this presentation are those of the speaker and not necessarily of the Food and Drug Administration

Agenda

- eCTD General Information & Advice
 - The Most Efficient Way to submit to FDA
 - Always Check before Submitting
- Formatting issues
 - Bookmarks, Hypertext links, Document formatting
 - Study Tagging Files (STFs)
 - Document Table of Contents (TOCs)
 - eCTD Placement and Leaf Titles
 - eCTD Operator Attributes
 - Granularity
- Final Take Away Message
- References
- Contact Information

eCTD: Electronic Common Technical Document

- eCTD is the standard electronic format for submissions to CBER and CDER
- eCTD format will be required in several years pending publication of final Guidance
- Reviewers want well formatted eCTD submissions
- Establishing standards helps increase efficiency!

Getting Started with eCTD

- Submit an eCTD sample for valuable feedback
- Transition existing applications to eCTD
- Become familiar with the information on the eCTD website and stay informed
- Send your eCTD questions to esub@fda.hhs.gov

eCTD: General Information & Advice

- Don't send additional paper copies when sending eCTD submissions
- Don't send files that aren't allowed (i.e., .zip, .exe, etc.)
- For submissions sent to the Central Document Room:
 - Refer to Transmission Specifications
 - Send media to the correct address
 - Ensure your media isn't blank or only contains empty folders

eCTD: General Information & Advice

- Once an eCTD always an eCTD means don't send non-eCTD or paper to an eCTD application
- Don't send files outside the eCTD sequence folder
- Don't send files that are not referenced in the correct, appropriate eCTD backbone (index.xml, us-regional.xml, stf.xml)
- Use the ANDA checklist to ensure the submission is complete
 - It's acceptable to provide an ANDA checklist indicating your submission's content
 - Providing reference links from the ANDA checklist to the information is helpful

The Most Efficient Way to Submit to FDA

- Use eCTD format
- Send via the Electronic Submissions Gateway (ESG)
- Include the correct/appropriate FDA fillable form (356h) and use digital signatures when signing the form

Benefits:

- Quick receipt and processing by FDA
- Quick access by reviewers
- Maximizes automation, reduces manual steps, minimizes chance of delays compared to alternative ways to submit
- In general, it's faster, easier, and better!

Always Check Your Submission

- Quality check (QC) your submission prior to submitting it
- Use checklists and establish a good, efficient QC process
- Ensure the media contains the submission
Ensure no files are truncated
 - Typically occurs when the path exceeds limits
 - Commonly occurs in m3-2-p-4 and m5-3-5-1 since some eCTD tools create folders from the metadata entered by the publisher/preparer



Create Your own Submission Checklist

Sample Submission Format Checklist¶

| | | |
|-------------------------------------|---|-------------------------------------|
| <input checked="" type="checkbox"/> | Application: 123456 | <input checked="" type="checkbox"/> |
| <input checked="" type="checkbox"/> | Drug Product Name is: _____ | <input checked="" type="checkbox"/> |
| <input type="checkbox"/> | Cover Letter (CL) | <input checked="" type="checkbox"/> |
| <input type="checkbox"/> | Signed FDA Form | <input checked="" type="checkbox"/> |
| <input type="checkbox"/> | CL, Form and eCTD Dates are correct and match or are within 1-2 days of each other | <input checked="" type="checkbox"/> |
| <input type="checkbox"/> | ANDA checklist: verified submission against the checklist, included the checklist, provided links to information when possible, | <input checked="" type="checkbox"/> |
| <input type="checkbox"/> | Admin Section Checks (us-regional.xml)¶ | <input checked="" type="checkbox"/> |
| <input type="checkbox"/> | · six-digit application number¶ | |
| <input type="checkbox"/> | · four-digit sequence number¶ | |
| <input type="checkbox"/> | · related sequence number (provide if submission is an amendment or resubmission) | |

| | |
|--------------------------|---|
| <input type="checkbox"/> | Documents and files Checks¶ |
| <input type="checkbox"/> | · Are in their correct location, if applicable (e.g., data)¶ |
| <input type="checkbox"/> | · Used meaningful leaf titles that indicate the document's content¶ |
| <input type="checkbox"/> | · Exact same leaf titles used for a document submitted in different file types includes the file type or other indicator to help differentiate between leaf titles. --¶ |
| <input type="checkbox"/> | · Referenced in correct backbones. ¶ |
| <input type="checkbox"/> | · Text is recognizable and can be search copied and pasted¶ |
| <input type="checkbox"/> | · Study files are referenced in the correct study's stf.xml file and tagged correctly¶ |
| <input type="checkbox"/> | · Physically reside in the correct location (i.e., stf.xml in the study's folder)¶ |
| <input type="checkbox"/> | · Files are accessible with good file names — no truncated files (search for ~ and ensure no file names have ~)¶ |
| <input type="checkbox"/> | · Documents exceeding 5 pages contain a Table of Contents (TOC)¶ |
| <input type="checkbox"/> | · Correct Page Rotation was applied (landscape or portrait)¶ |
| <input type="checkbox"/> | · Bookmarks exist and go to the correct destination¶ |
| <input type="checkbox"/> | · Bookmarks provided according to TOC¶ |
| <input type="checkbox"/> | · Bookmarks have good meaningful names that reflect the bookmark destination's content¶ |
| <input type="checkbox"/> | · Hyperlinks provided for references and they go to the correct destination¶ |
| <input type="checkbox"/> | · Hyperlinks appear as blue text or blue box links if blue text isn't possible¶ |
| <input type="checkbox"/> | · Proper lifecycle used on documents (replace, new, delete, append)¶ |

Bookmark Issues

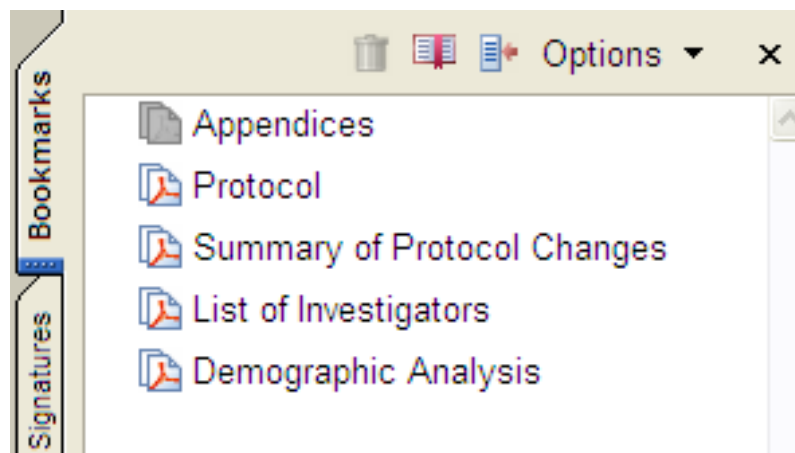
The following are considered bookmark issues:

- Not providing bookmarks
- Providing a few bookmarks when more are needed for navigating the document
- Providing bookmarks that don't have meaningful names (e.g., appendix 1, page 1, etc.)

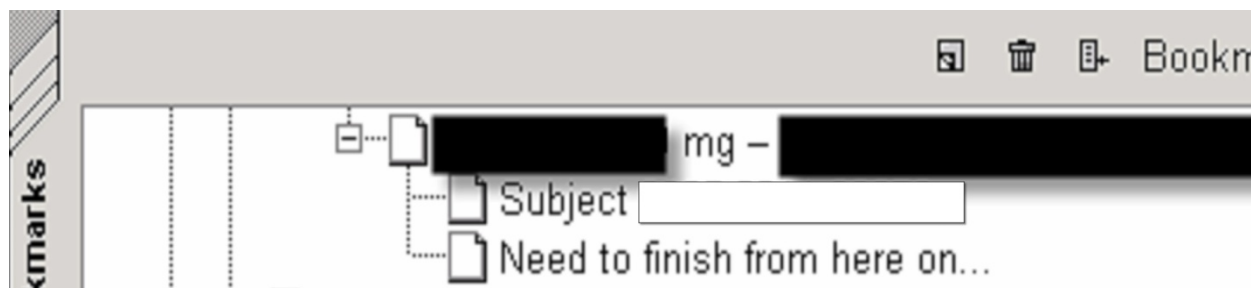
Please provide bookmarks and provide bookmarks with meaningful names!

Bookmark Issues

Good



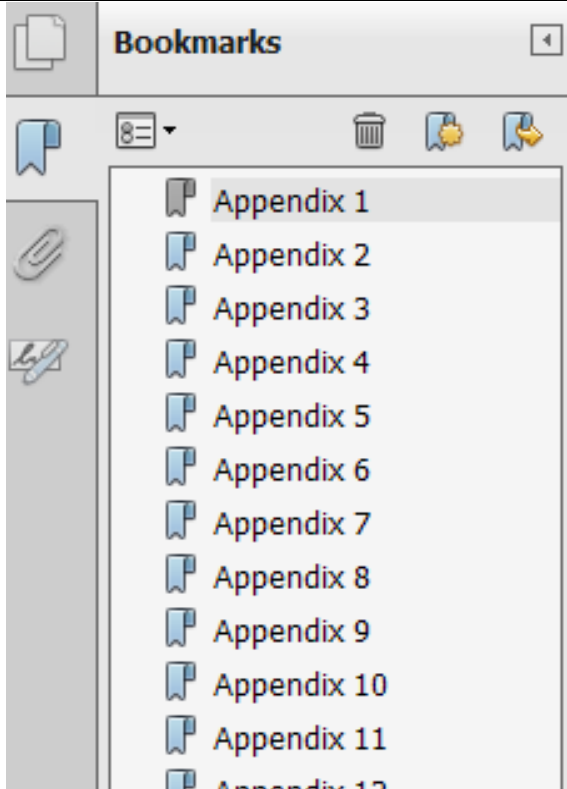
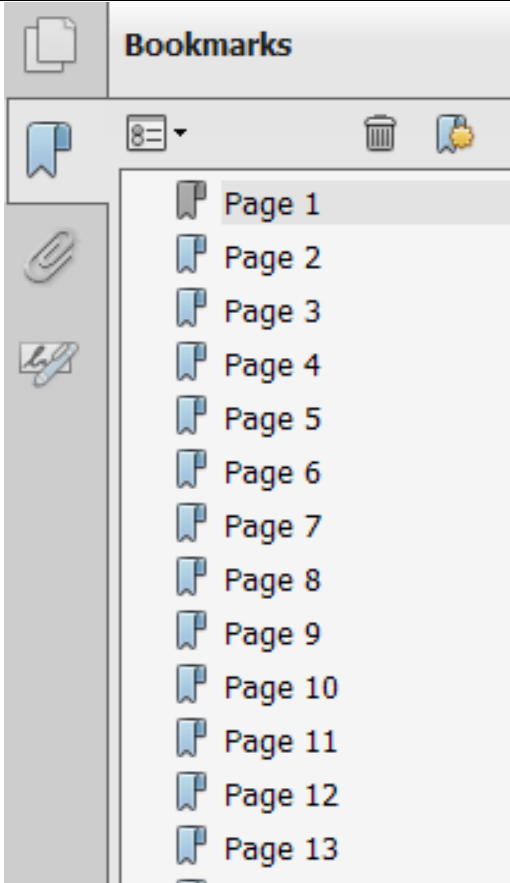
Bad



Examples of Bad Bookmarks

Bad

Really Bad

| Example 1: Bad Bookmarks | Example 2: More Bad Bookmarks |
|--|--|
|  <p>The screenshot shows a bookmarks toolbar with a list of 12 bookmarks. The first bookmark is highlighted. The list is labeled 'Appendix 1' through 'Appendix 12'.</p> |  <p>The screenshot shows a bookmarks toolbar with a list of 13 bookmarks. The first bookmark is highlighted. The list is labeled 'Page 1' through 'Page 13'.</p> |

Examples of Good Bookmarks

Bioequivalence Summary

Tables in m2-7

- BIOEQUIVALENCE SUMMARY TABLES**
 - Table 1 Submission Summary
 - Table 2 Summary of Bioavailability Studies
 - Table 3 Statistical Summary of the Comparative Bioavailability Data
 - Table 4 Bioanalytical Method Validation
 - Table 5 Summary of In Vitro Dissolution Studies
 - Table 6 Formulation Data
 - Table 7 Demographic Profile of Subjects Completing the Bioequivalence Study
 - Table 8 Incidence of Adverse Events in Individual Studies
 - Table 9 Reanalysis of Study Samples
 - Table 10 Study Information
 - Table 11 Product Information
 - Table 12 Dropout / Withdrawn Information
 - Table 13 Protocol Deviations
 - Table 14 Summaries of Standard Curve Data for Bioequivalence Sample

Protocol

- Bookmarks**
 - TABLE OF CONTENTS
 - LIST OF TABLES
 - 1. INTRODUCTION
 - 2. STUDY OBJECTIVES AND ENDPOINTS
 - 3. STUDY DESIGN
 - 4. SUBJECT SELECTION
 - 5. STUDY TREATMENTS
 - 6. STUDY PROCEDURES
 - 7. ASSESSMENTS
 - 8. ADVERSE EVENT REPORTING

Case Report Form (CRF)

- Bookmarks**
 - BY DOMAIN
 - BY VISIT
 - DATA CLARIFICATION FORMS

Bookmark Considerations

- Does the bookmark name indicate the bookmark's destination/content?
- Is the bookmark way too long?
- Are bookmarks provided for the TOC items?
- Does the bookmark match the description/title showing on the TOC?
- Will someone who is unfamiliar with the application will know what content they'll see before they click on the bookmark?
- Are bookmarks set to Inherit Zoom?
- If the answer to one or any of these questions is “no” then fix the bookmarks.

Hypertext Link Issues

- Insufficient hyperlinks (none or not enough)
- Hypertext links go to incorrect destination or don't work (destination set to same page)
- References aren't descriptive enough for a Reviewer to find the information if the link doesn't work or doesn't exist
- The Table of Contents (TOC) isn't linked
- For inter-document links, it's preferred that the link opens the other document in a new window
- Reviewers appreciate links instead of searching for a reference (table, figure, document, section, etc.)

Hypertext Link Recommendations

Provide linked references in documents (tables, figures, images, sections, inter-document links, etc.)

1. Provide clear, concise references.
2. Use blue text links (preferred) or blue box links
3. Providing linked references from the cover letter, Reviewers Guide or ANDA checklist is helpful
4. Provide linked TOCs in documents
5. Set links to Inherit Zoom
6. Check your links before submitting

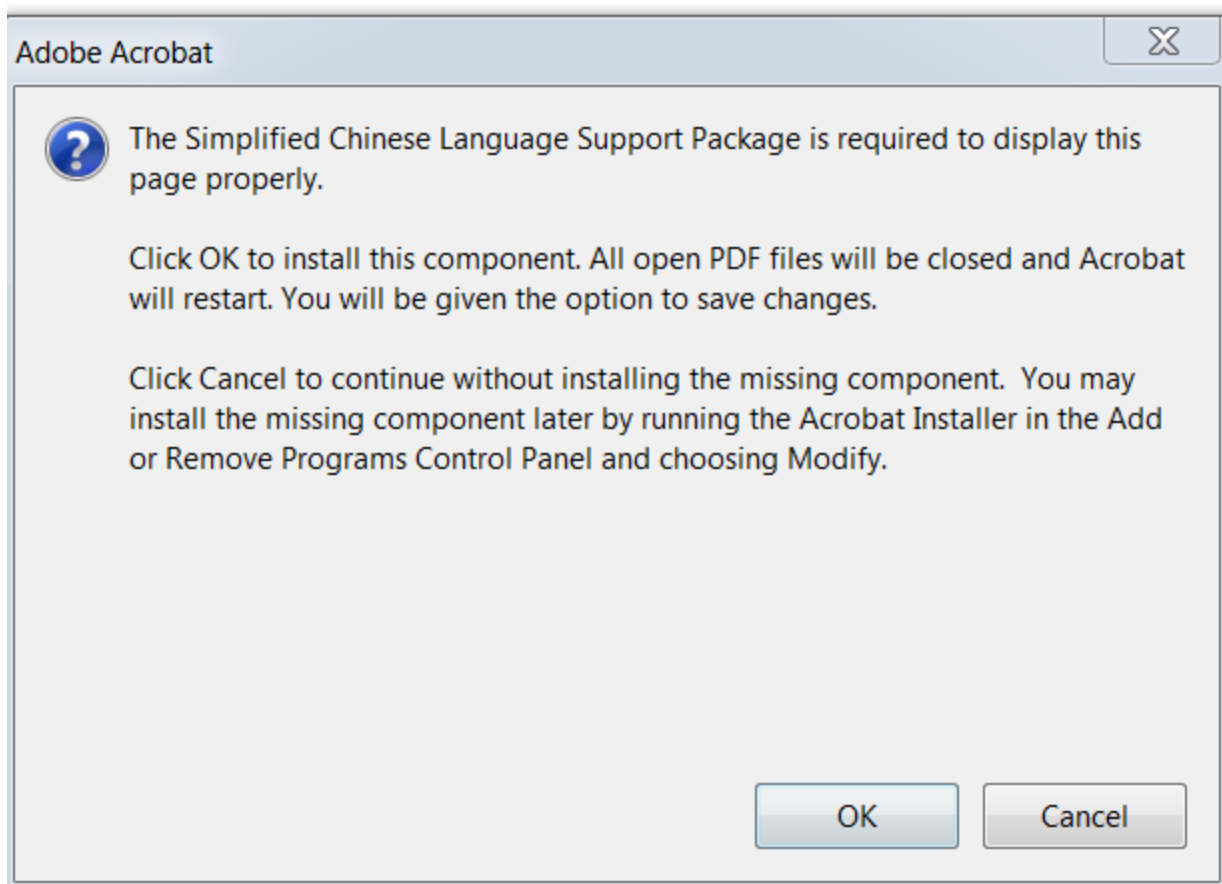
Document Recommendations

Provide:

- Correct page rotation (landscape or portrait)
- Use fonts 9 pt. Times New Roman or larger
- Legible documents- Adding a header or other information to a scanned document shouldn't affect or impact reviewability of the material
Documents with recognizable text for ease of copying and pasting
- Paginate documents
- Only use embedded fonts recommended in the PDF Specification

Document Font Error

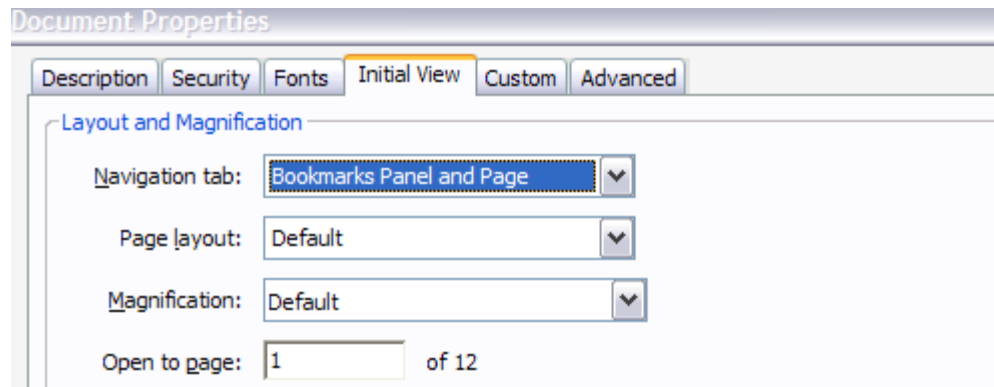
Avoid font errors to avoid resubmitting or replacing documents



Document Settings

Initial View Settings for PDFs:

- Navigation tab set to open to bookmarks, panel and page
- Page Layout set to default
- Magnification should be set default

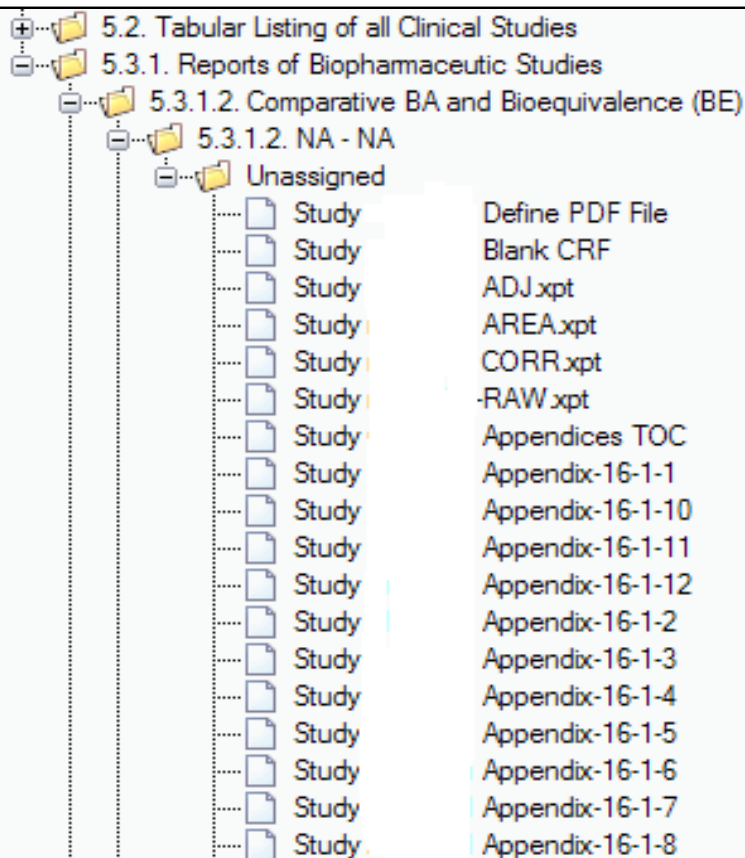


STFs Are Required For Studies

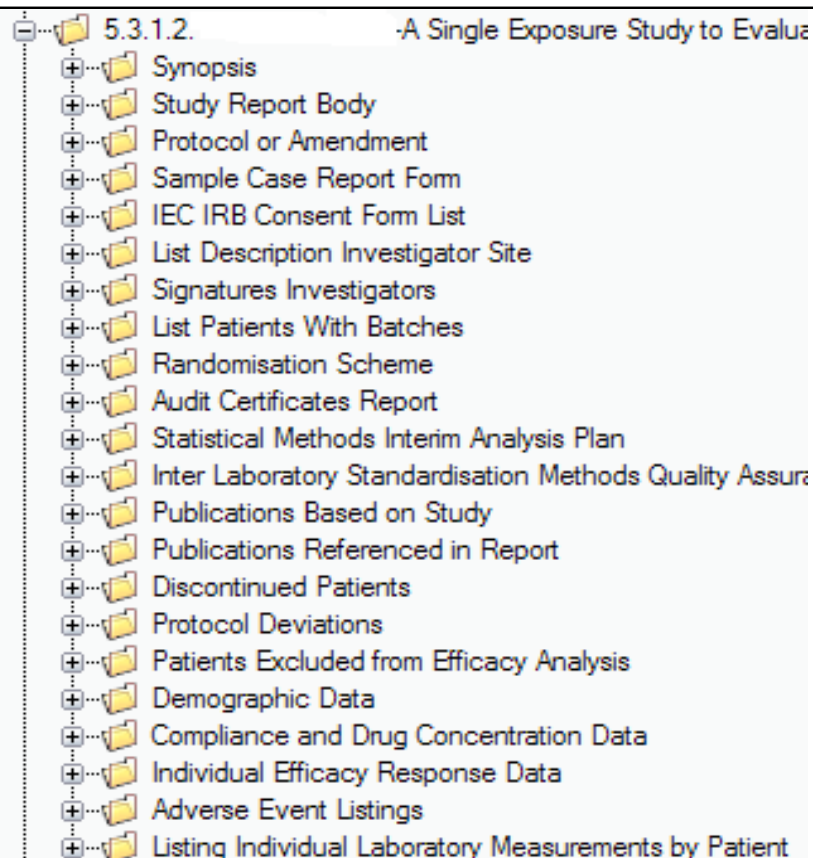
- Providing an STF for each study **is** necessary
- Applying correct study tagging files to each of the study's documents/files is necessary
- Please do it right the first time and every time thereafter
- Trying to correct or fix this issue can get very messy and it isn't quick or easy
- The study ID and study title shouldn't be the same – the title is usually much longer

STF.xml Files Organize Study Information

Bad Example- Failed to use an STF.xml and study tags



Good Example: Used an stf.xml for the study and applied study tags to the study's files



Recap STF Issues

- **Issues:**

- No STFs used for study documents and files
- STF used for **only some (not all)** of a study's files/documents (example: only used for CRFs) and/or doesn't include study tags

- **Solutions:**

- Ensure an STF is provided for each study and is placed in the study's main folder.
- **Reference every study file in its respective STF.xml file and ensure a valid, correct study tag is applied to every study's documents/files.**

eCTD Placement and TOCs in Documents

- **Issue:** Incorrect placement of information
- **Solution:** Refer to the eCTD CTOC and ANDA checklist
 - Review your submission using and checking navigation via leafs in the eCTD tree to ensure leafs are referenced in their respective, proper eCTD locations
- **Issues:** No TOC and/or no bookmarks provided for TOC items
- **Solution:** Provide TOC for documents exceeding 5 pages that contain multiple headings/sections, tables, figures and provide bookmarks according to the TOC.

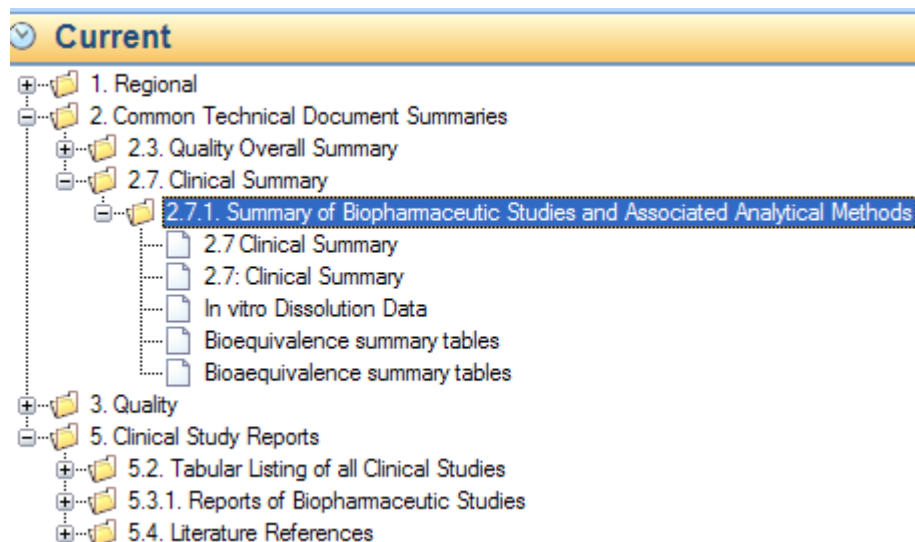
Leaf Title Issues

- **Issue:** Poor/bad leaf titles (i.e., Appendix 1.pdf, leaf title is only short file name instead of a descriptive, longer leaf title that indicates the document's content)
 - Is the leaf title indicative of the document's content?
 - Will someone who isn't familiar with the application know what the document is from the leaf title only without having to open the document?
 - Do the leaf titles exactly match the file name with .pdf in the leaf title?
- **Solution:** If the answer to the first two questions above is no or the answer to the third question is "yes", you should fix/correct the leaf titles.

Leaf Title Issues

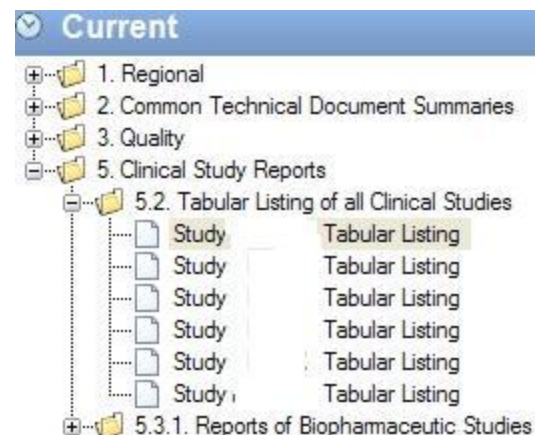
Issue: Same exact title used for multiple leaves

Solution: Include the file extension or type of application (MS Word) for non-PDF leafs



Issue: Provided one tabular listing for each study which resulted in multiple current tabular listings

Solution: Provide one PDF that includes a tabular listing of all studies



Operator Attribute Issues

- **Issue:** Incorrect use of eCTD operator attributes (i.e., fail to use/apply the replace operator resulting in multiple version of the same document when there should only be one current version)
 - Is there only one current version?
 - Will the reviewer expect to see and know why there are multiple current versions?
 - Will Reviewers know the difference between each current version from the leaf title?
- **Solution:** If the answer is “no”, you’re probably not using eCTD operator attributes correctly or you need to use leaf titles or another method to indicate the difference for the multiple current versions of a document.

ANDA Summary Bioequivalence Data

- Summary tables belong in m2-7

- Below is the link to the summary bioequivalence data table web page:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120962.htm>

- SAS / XPT data belongs in M5-3-1 referenced and tagged in the appropriate study's STF file

| Table | Name of Summary Data Table | Corresponding Module in eCTD | Corresponding Folder in eCTD | Corresponding Module/Section in paper CTD |
|-------|--|------------------------------|------------------------------|---|
| 1 | Submission Summary | m2 | 27-clin-Sum | 2.7.1.1 Background and Overview |
| 2 | Summary of Bioavailability (BA) Studies | m2 | 27-clin-Sum | 2.7.1.3 Comparison and Analysis of Results Across Studies |
| 3 | Statistical Summary of the Comparative BA Data | m2 | 27-clin-Sum | 2.7.1.3 Comparison and Analysis of Results Across Studies |
| 4 | Bioanalytical Method Validation | m2 | 27-clin-Sum | 2.7.1.1 Background and Overview |
| 5 | Summary of In Vitro Dissolution | m2 | 27-clin-Sum | 2.7.1.2 Summary of Results of Individual Studies |
| 6 | Formulation Data | m2 | 27-clin-Sum | 2.7.1.1 Background and Overview |
| 7 | Demographic Profile of Subjects Completing the Bioequivalence Study | m2 | 27-clin-Sum | 2.7.4.1.3 Demographic and Other Characteristics of Study Population |
| 8 | Incidence of Adverse Events in Individual Studies | m2 | 27-clin-Sum | 2.7.4.2.1.1 Common Adverse Events |
| 9 | Reanalysis of Study Samples | m2 | 27-clin-Sum | 2.7.1.2 Summary of Results of Individual Studies |
| 10 | Study Information | m2 | 27-clin-Sum | 2.7.1.1 Background and Overview |
| 11 | Product Information | m2 | 27-clin-Sum | 2.7.1.1 Background and Overview |
| 12 | Dropout Information | m2 | 27-clin-Sum | 2.7.1.2 Summary of Results of Individual Studies |
| 13 | Protocol Deviation | m2 | 27-clin-Sum | 2.7.1.2 Summary of Results of Individual Studies |
| 14 | Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis | m2 | 27-clin-Sum | 2.7.1.2 Summary of Results of Individual Studies |
| 15 | SOPs Dealing with Bioanalytical Repeats of Study Samples | m2 | 27-clin-Sum | 2.7.1.4 Appendix |
| 16 | Composition of Meal Used in Fed Bioequivalence Study | m2 | 27-clin-Sum | 2.7.1.3 Comparison and Analysis of Results Across Studies |

Document Granularity Issues

- **Issue:** You are providing many one page bioequivalence summary table documents when it would probably be more efficient for a reviewer to have one document with a TOC, bookmarks and links
- **Solution:** If it makes sense to combine one and two page documents into a single document in an eCTD section, then do it and provide a linked TOC with bookmarks.

The Final Take Away

Consider Your Audience: If you were the Reviewer and you are not familiar with the submission and application, could you easily navigate the submission and do an efficient review?

- Perform an overall QC after compiling the submission.
- Navigate the submission using eCTD TOC tree, leaf titles, links, and bookmarks keeping the reviewer in mind.
- Use a QC process or checklist to help ensure submissions don't contain formatting issues.
- Good planning and being proactive can help you avoid the need to respond to queries, send resubmissions, and send additional corrective submissions to fix formatting issues!

References

eCTD web page:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

eCTD CTOC (eCTD Table of Contents Headings and Hierarchy):

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>

PDF Specifications

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>

OGD web page:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm>

ANDA Check List:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM151259.pdf>



Contact Information

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